The Advantages of Segregation and the Evolution of Sex

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ABSTRACT

In diploids, sexual reproduction promotes both the segregation of alleles at the same locus and the recombination of alleles at different loci. This article is the first to investigate the possibility that sex might have evolved and been maintained to promote segregation, using a model that incorporates both a general selection regime and modifier alleles that alter an individual's allocation to sexual *vs.* asexual reproduction. The fate of different modifier alleles was found to depend strongly on the strength of selection at fitness loci and on the presence of inbreeding among individuals undergoing sexual reproduction. When selection is weak and mating occurs randomly among sexually produced gametes, reductions in the occurrence of sex are favored, but the genome-wide strength of selection is extremely small. In contrast, when selection is weak and some inbreeding occurs among gametes, increased allocation to sexual reproduction is expected as long as deleterious mutations are partially recessive and/or beneficial mutations are partially dominant. Under strong selection, the conditions under which increased allocation to sex evolves are reversed. Because deleterious mutations are typically considered to be partially recessive and weakly selected and because most populations exhibit some degree of inbreeding, this model predicts that higher frequencies of sex would evolve and be maintained as a consequence of the effects of segregation. Even with low levels of inbreeding, selection is stronger on a modifier that promotes segregation than on a modifier that promotes recombination, suggesting that the benefits of segregation are more likely than the benefits of recombination to have driven the evolution of sexual reproduction in diploids.

SEXUAL reproduction is widespread among eukaryotes (Bell 1982), but why sex evolved and why it is maintained in so many species have remained unresolved questions in evolutionary biology. Paradoxically, sexual reproduction, while common, entails several costs that are avoided by asexuals. Sexual organisms must find and court a mate, must risk disease transmission and predation during mating, and are prone to conflicts between the sexes, including conflicts over parental care (*e.g.*, a partner may contribute few resources to offspring production; Maynard Smith 1978) and conflicts over investment in current *vs.* future reproduction (Moore and Haig 1991; Chapman *et al.* 1995). A further problem with sexual reproduction is that it breaks up genetic associations that have accumulated over time in response to selection. In a constant environment without mutations or genetic drift, these genetic associations are typically favorable, and theoretical analyses have demonstrated that decreased levels of recombination evolve under such circumstances (Feldman 1972; Altenberg and Feldman 1987; Feldman *et al.* 1997). The resolution to the paradox of sex must, therefore, lie with perturbations—resulting from biotic or abiotic changes in the external environment, mutation, and/or random genetic drift within a population.

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Several theoretical studies have examined the evolution and maintenance of genetic mixing in the face of environmental change, mutation, and drift (see reviews by Barton and Charlesworth 1998; Otto and Michalakis 1998; West *et al.* 1999; Otto and Lenormand 2002), but these studies have largely ignored genetic associations within a locus under the assumption that sex evolved to promote recombination among alleles at different loci. Furthermore, those theoretical models investigating the evolution of rates of genetic mixing within a population (so-called "modifier models") have focused almost exclusively on the evolution of recombination rates. Yet sex entails the segregation of alleles at each locus as well as recombination between alleles at different loci. Just as recombination breaks up genetic associations among loci (linkage disequilibria), segregation breaks up genetic associations within a locus (departures from Hardy-Weinberg proportions). Thus, selection could indirectly favor the evolution of sexual reproduction through the effects of sex on one-locus genetic associations. Using a model that allows the allocation to asexual *vs.* sexual reproduction to depend on a modifier locus, this article investigates when we would expect increased sex to evolve as a consequence of segregation rather than recombination.

Within a randomly mating diploid species, sexual reproduction (meiosis followed by syngamy) breaks down associations between alleles carried on homologous chromosomes at a locus. Indeed, within a large, fully sexual

population exhibiting nonoverlapping generations, genetic associations at a locus are completely eliminated and Hardy-Weinberg proportions are attained after one generation of random mating. Within asexual populations or partially sexual populations, however, one-locus genetic associations can persist and accumulate over time. Whenever these genetic associations affect fitness, indirect selection will act on any feature that alters their accumulation, including the level of sexual reproduction. Genetic associations between two alleles (A and a) at a locus (**A**) are typically measured by the inbreeding coefficient, F, as

$$F = \frac{p_{AA} - p_A^2}{p_A p_a} = \frac{p_{AA}p_{aa} - (p_{Aa}/2)^2}{p_A p_a}, \quad (1)$$

where p_{ij} and p_k are the frequencies of genotype ij and allele k. As indicated by the first part of Equation 1, F measures the difference between the observed frequency of a genotype and its expected frequency at Hardy-Weinberg equilibrium. As indicated by the second part of Equation 1, F also measures whether homozygotes are more frequent ($F > 0$) or less frequent ($F < 0$) than expected based on the frequency of heterozygotes within the population. Thus, F can be thought of as a one-locus analog of the gametic-phase linkage disequilibrium (D), which measures whether combinations of alleles at two loci are more or less frequent than expected (see COMPARISONS TO OTHER MODELS AND INTERPRETATION). While F is called an "inbreeding coefficient," processes besides inbreeding can generate departures from $F = 0$, including selection and drift. While the associations between alleles at a locus generated by selection and drift would not persist in a fully sexual population, they do persist in a population that reproduces asexually as well as sexually.

With one exception (UYENOYAMA and BENGTSSON 1989, discussed below), all previous models that have investigated the importance of segregation to the evolution of sex have focused on mean fitness comparisons of sexual and asexual populations rather than examining the conditions under which sex evolves within a population. Let us begin by reviewing these mean fitness results, focusing on the three main forms of selection at a locus (heterozygote advantage, purifying selection, and directional selection). First, consider heterozygote advantage. Within an asexual population, the frequency of heterozygotes would rise to fixation, at which point there would be a strong negative one-locus genetic association ($F = -1$). Within a sexual population, however, the segregation of alleles would break down the genetic association, and the less fit homozygotes would be formed by syngamy each generation. Hence, at equilibrium, a sexual population would suffer a decrease in mean fitness, known as the "segregation load," compared to an asexual population (CROW 1970; PECK and WAXMAN 2000).

Second, consider purifying selection acting against mutant alleles at a locus. Within a population containing both wild-type (A) and mutant (a) alleles, the relative fitness of a diploid individual can be written as

$$\text{Fitness}(AA) = 1, \quad \text{Fitness}(Aa) = 1 - hs, \quad \text{Fitness}(aa) = 1 - s, \quad (2a)$$

where s is the selection coefficient ($0 < s \leq 1$) and h is the dominance coefficient ($0 \leq h \leq 1$). The dominance coefficient, h, measures one-locus fitness interactions on an additive scale. An alternative coefficient that plays a more central role in the evolution of sex measures dominance on a multiplicative scale:

$$\iota = \text{Fitness}(AA)\text{Fitness}(aa) - \text{Fitness}(Aa)^2 = -s(1 - 2h + h^2 s). \quad (2b)$$

On a log scale, ι measures whether homozygotes are more fit ($\iota > 0$) or less fit ($\iota < 0$) than expected based on the fitness of heterozygotes. Note that ι can be thought of as a one-locus analog of epistasis (ε), which is a measure of fitness interactions between alleles at two loci (see COMPARISONS TO OTHER MODELS AND INTERPRETATION). If mutations recur at frequency μ per gamete per generation and if mating is random among individuals reproducing sexually, the equilibrium frequency of Aa individuals is $\sim 2\mu/(hs)$ in both asexual and sexual diploid populations (assuming weak mutation, $\mu \ll hs$). The mean fitness is then $\sim 1 - 2\mu$. A more exact treatment that keeps track of order μ^2 terms (CHASNOV 2000) indicates, however, that a negative genetic association (F) develops whenever

$$\iota < 0 \quad (3a)$$

or, equivalently,

$$h < \frac{1}{1 + \sqrt{1 - s}}. \quad (3b)$$

Thus, when homozygotes are relatively less fit ($\iota < 0$), a departure from Hardy-Weinberg develops such that there are fewer homozygotes than expected at equilibrium ($F < 0$). This one-locus genetic association reduces the genetic variance in fitness, which hinders selection and slightly reduces the mean fitness at equilibrium. Segregation breaks down this detrimental association, causing sexual populations to have a slightly higher mean fitness than asexual populations at equilibrium (CHASNOV 2000). Conversely, when homozygotes are relatively more fit ($\iota > 0$), homozygotes become more common then expected ($F > 0$), which slightly increases genetic variance in fitness and the mean fitness at equilibrium. Now, the one-locus genetic associations built up by selection are favorable. Consequently, the mean fitness at equilibrium is higher in asexual populations, which preserve these associations, than in sexual popula-

tions. Typically, data on dominance suggest that deleterious mutations are partially recessive ($h < ½$; Simmons and Crow 1977; Deng and Lynch 1997; Garcia-Dorado *et al.* 1999). Thus, we expect (3) to hold and predict that sexual populations should have a higher equilibrium mean fitness than asexual populations. As long as sex involves random mating, this advantage is negligibly small unless deleterious mutations are very recessive ($\mu/s \leq h \leq \sqrt{\mu/s}$; Chasnov 2000). When sexual reproduction is accompanied by inbreeding (the union of gametes that are closely related by descent), however, homozygotes become more common than expected at Hardy-Weinberg equilibrium, causing the mean fitness of sexual populations to be substantially higher than that of asexual populations (Agrawal and Chasnov 2001).

Third, consider directional selection causing the spread of a favored allele, *A*, within a population. Although it is nonstandard, I continue to use the fitness regime described by (2) as this makes it easier to recognize parallels between the results with purifying and directional selection. The arguments made in the previous paragraph continue to apply when genetic associations are initially absent but are generated by directional selection. That is, if (3) holds, selection will cause homozygotes to become less common than expected, decreasing the genetic variance and slowing down adaptive evolution. By breaking down the one-locus genetic associations, sexual reproduction speeds up selection and gains a long-term advantage. Conversely, if (3) fails to hold, selection generates excess homozygosity, a genetic association that hastens adaptive evolution. Now, by breaking down the associations, sexual reproduction hinders selection and suffers a long-term disadvantage. This argument assumes that all genotypes are initially present. Imagine instead that *A* arises as a single mutation in a heterozygous individual. The spread of the favorable allele would then be limited to the fixation of the heterozygote within asexual populations, at which point adaptive evolution would stall until the *AA* homozygote was generated by a second mutation or mitotic recombination (Kirkpatrick and Jenkins 1989). In contrast, the *AA* homozygote would be produced immediately by segregation within sexual populations, hastening adaptation and providing sexual populations with a long-term fitness advantage over asexual populations (Kirkpatrick and Jenkins 1989).

The above discussion focuses on the effects of selection on one-locus genetic associations (F) and long-term mean fitness within an asexual population or a sexual population. These results can predict the outcome of competition between sexual and asexual populations, but only if the sexual and asexual populations are ecologically equivalent yet have been reproductively isolated for long enough for genotypes to reach the frequencies expected under each mode of reproduction. To fully understand the evolution of sex, however, we must also ask how the frequency of sex evolves within a population that is capable of both sexual and asexual reproduction, as is common among protists, fungi, algae, plants, and several invertebrate animal groups (Bell 1982). This article addresses this question by tracking the frequency of alleles that modify the relative allocation to the two modes of reproduction within a single population. Alleles at such a "modifier" locus (**M**) could act in any number of ways; for example, they could alter the probability of undergoing mitotic *vs.* meiotic cell division in unicellular organisms or alter the probability of reproducing via fission, budding, or apomixis in multicellular organisms.

In this article, evolution at the modifier locus is examined with respect to the dynamics at a locus, **A**, subject to either purifying or directional selection, which exhibit qualitatively similar results. For want of a better term, the **A** locus is called a "fitness locus." In a companion article, we examine the evolution of sex when the fitness locus is subject to heterozygote advantage (Dolgin and Otto 2003, this issue), where, to our surprise, we also found that a modifier that increases the frequency of sex can spread under reasonable sets of parameters. A similar model was analyzed by Uyenoyama and Bengtsson (1989), although they restricted their attention to lethal deleterious mutations; their results are summarized where parallels exist to this article. As we shall see, evolutionary change at the modifier locus depends strongly on the degree of inbreeding within the population and the degree of dominance and strength of selection at fitness loci. I argue that, for biologically reasonable values of these parameters, selection generally favors the evolution of increased levels of sexual reproduction and that such selection is strong relative to other deterministic forces acting on the evolution of sex.

MODEL

Consider two loci, a modifier locus **M** and a fitness locus **A**, within a diploid population with nonoverlapping generations. To track changes in allele frequencies at these loci, we begin by censusing at the juvenile stage, before selection, and then proceed through selection, mutation, and reproduction. Let x_{ij} equal the frequency of juveniles that carry haplotypes i and j (where i and j equal 1 for haplotype *MA*, 2 for *Ma*, 3 for *mA*, and 4 for *ma*). I assume that all loci are autosomal, that selection does not depend on the sex of the parent, and that there is no selection at the haploid or gametic stage. Consequently, I assume that $x_{ij} = x_{ji}$ and keep track of x_{ij} for $j \geq i$, only. Thus, for example, the frequency of *MM AA* individuals is x_{11} but the frequency of *MM Aa* individuals is $2x_{12}$. At this point, selection occurs according to Equation 2. Let $\tilde{x}_{ij}$ equal the frequency after selection of adults carrying haplotypes i and j. Thus,

$$\tilde{x}_{11} = x_{11}/\overline{W} = \text{Frequency}(MM\,AA) \text{ after selection}$$

$$2\tilde{x}_{12} = 2x_{12}(1 - hs)/\overline{W} = \text{Frequency}(MM\,Aa) \text{ after selection,}$$

etc., where $\overline{W}$ is the mean fitness within the population. At this stage, mutations from allele A to a occur at rate μ, regardless of the mode of reproduction. Mutations from allele a to A may also occur, but they are ignored because, at mutation-selection balance, allele a is so rare that the frequency of revertants to A is vanishingly small. In the case of a favorable allele spreading through a population, mutations assert a very small influence on the dynamics and are ignored. Let $\tilde{\tilde{x}}_{ij}$ equal the genotype frequencies after selection and mutation, where

$$\tilde{\tilde{x}}_{11} = (1 - \mu)^2\tilde{x}_{11} = \text{Frequency}(MM\,AA) \text{ after mutation and selection,}$$

$$2\tilde{\tilde{x}}_{12} = 2(1 - \mu)\tilde{x}_{12} + 2\mu(1 - \mu)\tilde{x}_{11} = \text{Frequency}(MM\,Aa) \text{ after mutation and selection,}$$

etc.

At this point, reproduction occurs. The probability that an individual reproduces sexually depends on its genotype at the modifier locus, **M**:

Genotype:	*MM*	*Mm*	*mm*
Probability of sex:	σ_1	σ_2	σ_3

If an individual of genotype ij does not reproduce sexually, which occurs with probability $1 - \sigma$, then it contributes directly to the frequency of juveniles of genotype ij in the next generation (x'_{ij}). If the individual reproduces sexually, meiosis occurs with recombination between the **M** and **A** loci at rate r. In many organisms with both sexual and asexual reproduction, including most sexual protists, fungi, algae, and nonseed plants, sex involves an alternation of generations between haploid and diploid phases (Bell 1982). I thus assume that meiosis generates haploid gametophytes, among whom the frequency of haplotype i is given by y_i. The frequency of *MA* haploids, for example, would be

$$y_1 = \frac{\sigma_1(\tilde{\tilde{x}}_{11} + \tilde{\tilde{x}}_{12}) + \sigma_2(\tilde{\tilde{x}}_{13} + \tilde{\tilde{x}}_{14}(1 - r) + \tilde{\tilde{x}}_{23}r)}{\overline{\sigma}}, \quad (4)$$

where $\overline{\sigma}$ is the average allocation of the diploid population to sexual reproduction,

$$\overline{\sigma} = \sigma_1(\tilde{\tilde{x}}_{11} + 2\tilde{\tilde{x}}_{12} + \tilde{\tilde{x}}_{22}) + \sigma_2(2\tilde{\tilde{x}}_{13} + 2\tilde{\tilde{x}}_{14} + 2\tilde{\tilde{x}}_{23} + 2\tilde{\tilde{x}}_{24}) + \sigma_3(\tilde{\tilde{x}}_{33} + 2\tilde{\tilde{x}}_{34} + \tilde{\tilde{x}}_{44}). \quad (5)$$

The haploid phase is assumed to be limited in scope, and selection in this phase is ignored. Genetically identical gametes are then produced by each haploid. The probability that any two gametes unite to form a zygote depends on the mating system. In this model, gametes undergo random union with probability $1 - f$ or inbreed with probability f. Random union produces diploids of genotype ij with probability y_iy_j. Inbreeding occurs among the gametes of a haploid gametophyte, resulting in the production of genotype ii from haploids of genotype i with probability y_i. I refer to this form of inbreeding as gametophytic selfing (this corresponds to "intragametophytic selfing" in the terminology of Klekowski 1969). Gametophytic selfing is only one mechanism by which inbreeding can occur. Inbreeding also occurs when there is sporophytic selfing (where the gametes of a diploid adult are mixed at random), mating among kin, and/or spatial population structure. It is important to keep in mind that the rate of inbreeding (f) is a measure of who mates with whom, whereas the inbreeding coefficient (F) measures a departure from Hardy-Weinberg proportions regardless of the cause of this departure. While all forms of inbreeding generate an excess of homozygosity (positive F), gametophytic selfing does this to the greatest degree (100% of offspring are homozygous). Nevertheless, it is expected that qualitatively similar results to the current model would be observed with other mechanisms of inbreeding.

The overall contribution to the juveniles of the next generation through sexual reproduction is then weighted by the population's average allocation to sex, $\overline{\sigma}$. Thus, the frequency of *MM AA* juveniles in the next generation equals

$$x'_{11} = (1 - \sigma_1)\tilde{\tilde{x}}_{11} + \overline{\sigma}\,(y_1^2(1 - f) + y_1f), \quad (6a)$$

and the frequency of *MM Aa* juveniles (including both 12 and 21 genotypes) in the next generation equals

$$2x'_{12} = (1 - \sigma_1)2\tilde{\tilde{x}}_{12} + \overline{\sigma}(2y_1y_2(1 - f)). \quad (6b)$$

Recursion equations (6c)–(6j) for the remaining diploid juveniles were derived similarly (available upon request). Table 1 summarizes the notation. For the case of $s = 1$, these recursions are identical to those developed by Uyenoyama and Bengtsson (1989) when inbreeding is absent ($f = 0$) but differ when inbreeding is present, because they assume sporophytic selfing rather than gametophytic selfing.

Throughout the analyses, the recursions (6) are used to determine when a modifier that increases the frequency of sex would spread within a population. To begin, I analyze the case where the population is at a mutation-selection balance at the **A** locus with the M allele fixed at the modifier locus. I then determine the conditions under which a new modifier allele, m, can spread if it alters the level of sex within the population. The results differ substantially depending on whether or not there is inbreeding (*i.e.*, $f = 0$ or $f \neq 0$), so these cases are discussed in turn. Next, I turn to the case of directional selection where a beneficial allele, A, is increasing in frequency within a population, assuming that mutation is a negligible force. Finally, connections are drawn between the results of this model of segregation and models of recombination and ploidy evolution. *Mathematica* 3.0 (Wolfram 1991) packages that were

TABLE 1

Summary of notation

p_A, p_a	Frequencies of the favorable (A) and deleterious (a) alleles at the fitness locus **A**
p_M, p_m	Frequencies of the current (M) and new (m) alleles at the modifier locus **M**
F	Inbreeding coefficient that measures excess homozygosity (Equation 1)
D	Linkage disequilibrium between two loci
s	Selection coefficient acting against allele a (Equation 2)
h	Dominance coefficient of allele a measured on an additive scale (Equation 2)
ι	Dominance coefficient of allele a measured on a multiplicative scale ($= 2hs - s - h^2s^2$)
μ	Mutation rate from allele A to allele a per generation
L	Number of loci per genome
U	Mutation rate to deleterious alleles per diploid genome per generation ($= 2\mu L$)
σ_i	Probability that a diploid reproduces sexually, where $i = 1$ for MM, 2 for Mm, and 3 for mm genotypes at the modifier locus
$\Delta\sigma$	The homozygous effect of the M modifier allele on the probability of sex ($\sigma_3 - \sigma_1$)
h_M	The dominance coefficient of the M modifier allele ($\sigma_2 = \sigma_1 + h_M\,\Delta\sigma$)
$\delta\sigma$	The allelic effect of an additive modifier ($\sigma_2 = \sigma_1 + \delta\sigma$; $\sigma_3 = \sigma_1 + 2\delta\sigma$)
f	Selfing (inbreeding) rate among gametes (Equation 6)
r	Recombination rate between loci **A** and **M**
x_{ij}	Frequency of juvenile diploids carrying haplotypes i and j, where Index (i, j): 1 2 3 4 Denotes haplotype: MA Ma mA ma
$\hat{x}_{ij}$, $\tilde{x}_{ij}$, x'_{ij}	Frequency of the ij genotype after selection, mutation, and a full generation
y_i	Frequency of haplotype i among the haploid offspring of sexually reproducing diploids
c_i	Function whose sign is never negative (see Table 2)
d_i	Function whose sign depends on the parameter values (see Table 2)
θ	Cutoff between regions in which sex is favored
ϕ (Φ)	Indirect selection on the modifier resulting from the modifier's effects on segregation at one locus (across the genome)
Ψ	Direct selection on the modifier resulting from the cost of sex
δ	The cost of sex

used to derive the results and to perform numerical analyses are available upon request.

Mutation-selection balance: *The equilibrium:* When allele M is fixed, the recursions (6) reach a mutation-selection balance at which the AA genotype predominates as long as selection is stronger than mutation. Throughout, I assume that mutation is a weak force, that inbreeding, when present, is large relative to the mutation rate ($f \gg \mu$), and that hs and fs are not both small relative to μ. At equilibrium, genotypic frequencies remain constant ($x'_{ij} = x_{ij}$), and I denote the equilibrium frequencies by $\hat{x}_{ij}$. To find $\hat{x}_{ij}$, assume that mutation is rare, allowing us to expand and solve $\hat{x}_{ij}$ in terms of μ. With M fixed, only three genotypes are present, and their frequencies at equilibrium are, to order μ^2,

$$\begin{aligned}
\hat{x}_{11} &= 1 - 2\hat{x}_{12} - \hat{x}_{22}\\
\hat{x}_{12} &= \frac{\mu c_1}{sc_2} - \frac{\mu^2 c_1}{s^2 c_2^3}\Big(h^2 s(1-f)\sigma_1 c_1 + (c_1 h - 2\sigma_1 h(1-f))\\
&\qquad (c_0 - fs\sigma_1) + \sigma_1(c_1 + fc_0)\Big) + O(\mu^3)\\
\hat{x}_{22} &= \frac{\mu f\sigma_1}{sc_2} - \frac{\mu^2 hc_1}{s^2 c_2^3}\,(h^2 s^2(1-\sigma_1)c_1\\
&\qquad - hs(2c_0 - 2c_1\sigma_1 - 3fc_0\sigma_1 + f^2\sigma_1^2)\\
&\qquad - \sigma_1(c_1 + 2fc_0 - sf^2\sigma_1)) + O(\mu^3). \qquad (7)
\end{aligned}$$

Here and throughout this article, c_i denotes a function, defined in Table 2, that is positive (or zero) under the stated assumptions. These functions do not necessarily have any biological meaning and are used solely to simplify the presentation of the equations. Note that when inbreeding is absent ($f = 0$), c_1/c_2 is $1/h$, and $\hat{x}_{12}$ equals the familiar $\mu/(hs)$ plus terms of order μ^2.

At this mutation-selection balance, one-locus genetic associations are generated by both selection and inbreeding. When mating is random (*i.e.*, no selfing; $f = 0$), the one-locus genetic association calculated at the equilibrium described by Equation 7 equals

$$\hat{F}_{f=0} = \iota\,\frac{\mu}{hs}\left(\frac{1-\sigma_1}{1-(1-\sigma_1)(1-s)}\right) + O(\mu^2), \qquad (8)$$

where $O(\mu^2)$ denotes terms of the order μ^2 or smaller. Thus, as found by Chasnov (2000), the sign of ι determines the sign of $\hat{F}_{f=0}$ (see Equations 2 and 3). When ι is negative, the genotypes with the more extreme fitness (AA and aa) have a lower mean fitness on a log scale than the intermediate genotypes (Aa) and consequently become underrepresented within the population ($\hat{F}_{f=0}$ becomes negative), with the reverse holding when ι is positive.

Selfing and other forms of inbreeding ($f > 0$) generate a positive one-locus genetic association,

$$\hat{F}_{f>0} = f\frac{\sigma_1}{1-(1-\sigma_1)(1-s)} + O(\mu). \qquad (9)$$

TABLE 2

Functions used to simplify the equations

$$c_0 = 1 - (1 - \sigma_1)(1 - s)$$
$$c_1 = s(1 - \sigma_1) + \sigma_1(1 - f)$$
$$c_2 = hc_0 + f\sigma_1(1 - h)$$
$$c_3 = 1 - (1 - \sigma_2)(1 - s)$$
$$c_4 = 1 - (1 - \sigma_2)(1 - hs)$$
$$c_5 = 1 - (1 - r\sigma_2)(1 - hs)$$
$$c_6 = r^2(s + 2\sigma_2)^2 + 4rs(\sigma_2(1 - 2r\sigma_2) + s(1 - \sigma_2)(1 - r\sigma_2))$$
$$c_7 = 1 - (1 - \sigma_3)(1 - s)$$
$$c_8 = 1 - (1 - \sigma_3)(1 - hs)$$
$$d_0 = (hs)^2(\sigma_2(1 - 2r\sigma_2) + s(1 - \sigma_2)(1 - r\sigma_2)) + (hs)r\sigma_2(s + 2\sigma_2) - rs\sigma_2^2$$

$$d_1 = (1 - f)^2\,\sigma_1(\sigma_3 - \sigma_2)\left(c_7\left(\frac{1}{2} - r\right)(1 - hs)\sigma_2(c_4d_2 + 2(1 - h)hs\sigma_3) + \frac{1}{2}c_4(c_7hs(hs + (1 - hs)(2\sigma_2 - \sigma_3)) - c_4c_7d_2 - 2(1 - h)(1 - s)hs\sigma_3^2)\right)$$
$$- (1 - f)sc_4\left(d_2\left(\frac{1}{2} - r\right)(1 - hs)\sigma_2^2(\sigma_3 - \sigma_1) + h\sigma_1(\sigma_3 - \sigma_2)(c_4c_7 + (1 - h)s\sigma_3) + \frac{1}{2}\sigma_2(\sigma_3 - \sigma_1)(hs(2c_4 - d_2 - 2(1 - h)\sigma_3) - c_4d_2)\right) + c_4^2hs^2\sigma_2(\sigma_3 - \sigma_1)$$

$$d_2 = hs(1 - \sigma_3) + (2h - 1)\sigma_3$$
$$d_3 = 1 - 2h - 2hs + 2h^2s$$

For weak selection, the inbreeding coefficient given by (9) approaches f, as expected for a neutral locus under gametophytic selfing. Note that the one-locus genetic association will typically be orders of magnitude larger when generated by nonrandom mating (9) than when generated by selection alone (8).

Stability analysis without inbreeding: To determine whether a modifier allele that alters an organism's reproductive allocation (σ) to sexual *vs.* asexual reproduction will invade or disappear when introduced at low frequency within a population, I performed a local stability analysis on the recursions (6) in the vicinity of the equilibrium (7) (for a primer on stability analysis, see Appendices in Bulmer 1994 or Roughgarden 1979). The fate of a rare modifier allele (m) depends on the eigenvalues (λ) of the local stability matrix of (6). If all eigenvalues are less than one in magnitude, the m allele declines in frequency over time. Conversely, if at least one eigenvalue is greater than one, allele m will spread within the population. Without inbreeding ($f = 0$), invasion of the modifier allele at a geometric rate is predicted to occur only when the following eigenvalue is greater than one:

$$\lambda_{f=0} = 1 - \mu^2(\sigma_2 - \sigma_1)\frac{\iota d_0}{h^2s^2c_0c_3c_4c_5} + O(\mu^3). \quad (10)$$

In contrast to c_i, the d_i denote functions (also defined in Table 2) that are known to change sign depending on the parameter values. If the new modifier allele, m, increases the frequency of sex ($\sigma_2 > \sigma_1$), it will invade if $\lambda_{f=0}$ is greater than one, which requires that $\iota < 0$ and $d_0 > 0$. In other words, there must be an intermediate level of dominance for sex to be favored:

$$\frac{2r\sigma_2}{2r\sigma_2 + rs + \sqrt{c_6}} < h < \frac{1}{1 + \sqrt{1 - s}}. \quad (11)$$

The parameter range in which sex is favored shrinks as selection becomes weaker, with both the left- and right-hand side of (11) approaching ½ as s goes to zero. Sex is favored over the broadest range of parameters when deleterious mutations are lethal ($s = 1$), in which case modifiers that increase allocation to sexual reproduction spread for all dominance coefficients with tight linkage ($r = 0$) and for $h > \sigma_2/(2 + \sigma_2)$ with loose linkage ($r = ½$). For lethal deleterious mutations ($s = 1$), Equation 11 is equivalent to Equation A2.2a in Uyenoyama and Bengtsson (1989). Although (11) appears not to depend on the current level of sex (σ_1), the inequalities are easiest to satisfy when the modifier causes *Mm* heterozygotes to engage in a low frequency of sex (small σ_2), which requires that the initial population be primarily asexual for the modifier to increase the frequency of sex ($\sigma_2 > \sigma_1$). For dominance coefficients outside of the range given by (11), selection favors a decreased level of sex. These conditions are illustrated in Figure 1. Considering the case of weak selection and partial recessivity of deleterious mutations as the most biologically relevant, these results indicate that modifiers that increase the frequency of sex would be selected against when inbreeding is absent. The strength of this selection is, however, extremely weak ($O(\mu^2)$).

Stability analysis with inbreeding: Inbreeding dramatically alters the conditions under which sex is favored by uncoupling the sign of the genetic associations (F) from the form of selection (compare Equations 8 and 9). A second local stability analysis was performed to deter-

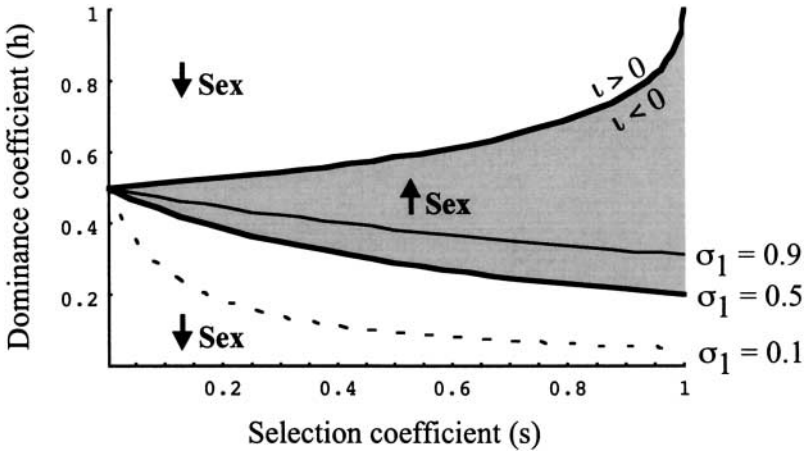

FIGURE 1.—Conditions under which a rare modifier that changes the frequency of sex without inbreeding ($f = 0$) spreads within a population based on Equation 10. Along the topmost curve, there are multiplicative fitness interactions within a locus ($\iota = 0$). For $\sigma_1 = 0.5$, modifiers that increase the frequency of sex spread only in the shaded region, *i.e.*, when ι is negative but weak. This region expands in less sexual populations ($\sigma_1 = 0.1$; dashed curve) and contracts in more sexual populations ($\sigma_1 = 0.9$; thin solid curve). Other parameters are $\sigma_2 = \sigma_1 + 0.01$, $r = \frac{1}{2}$.

mine when evolution favors an increase in the frequency of sexual reproduction given that sex involves selfing or inbreeding ($f > 0$). The analysis indicates that a new modifier allele spreads at a geometric rate only when the following eigenvalue is greater than one:

$$\lambda_{f>0} = 1 + \mu \frac{fd_1}{c_2c_4c_8(\sigma_2 f + \sigma_3(1-f))(c_5c_7(1-f) + c_4 sf)} + O(\mu^2). \quad (12)$$

Invasion thus requires that d_1 be positive.

Figures 2–4 illustrate the conditions under which a modifier that increases the frequency of sex is able to spread. The evolution of sexual reproduction is favored in two regions. In region 1, selection is weak and deleterious mutations are recessive (bottom left-hand sides in Figures 2–4), and in region 2, selection is strong and deleterious mutations are dominant (top right-hand sides in Figures 2–4).

In examining the figures, I noted that, for each combination of parameters, there was a value of s, at which, simultaneously, the curve delimiting region 1 crossed the $h = 0$ axis and the curve delimiting region 2 crossed the $h = 1$ axis. At this exact point, called θ, sex was never favored, regardless of the dominance coefficient (*e.g.*, θ occurs at $s = 0.31$ in Figure 4). Because the leading eigenvalue equals one along these curves, I determined the value of θ by setting h to either 0 or 1 (the result was the same) in (12) and solving $\lambda_{f>0} = 1$ for s, obtaining

$$\theta = \frac{(1-f)\sigma_1\sigma_3(\sigma_3 - \sigma_2)}{\sigma_1\sigma_3(\sigma_3 - \sigma_2) + \sigma_3(\sigma_2 - \sigma_1) + f\sigma_1(1-\sigma_3)(\sigma_3 - \sigma_2)}. \quad (13)$$

θ, which marks the boundary between regions 1 and 2, varies as a function of the frequency of sex (σ_i, explored in Figure 2) and the level of inbreeding (f, explored in Figure 3), but it is constant as a function of the rate of recombination between the modifier and fitness loci (r, explored in Figure 4). Note that the cutoff θ lies between zero and one for "directional modifiers," a term that I use to denote a modifier allele, m, that increases the frequency of sex ($\sigma_1 \le \sigma_2 \le \sigma_3$) or decreases it ($\sigma_1 \ge \sigma_2 \ge \sigma_3$).

Equation 13 allows us to determine how the cutoff between regions in which sex is favored varies with changing parameter values. For the following, I assume that the modifier is directional and define $\sigma_2 = \sigma_1 + h_M\Delta\sigma$ and $\sigma_3 = \sigma_1 + \Delta\sigma$, where $\Delta\sigma$ measures the homozygous effect of the modifier allele on the frequency of sex and h_M ($0 \le h_M \le 1$) measures the dominance of the modifier. From (13), it can be shown that

i. $d\theta/df \le 0$. Higher rates of selfing/inbreeding decrease the cutoff, making it less likely that weakly selected, partially recessive mutations favor sex (see Figure 3).
ii. $d\theta/d\Delta\sigma \ge 0$. Stronger modifiers increase the cutoff, making it more likely that weakly selected, partially recessive mutations favor sex.
iii. $d\theta/dh_M < 0$. More dominant modifiers decrease the cutoff, making it less likely that weakly selected, partially recessive mutations favor sex. In the special case of a fully dominant modifier, the cutoff goes to zero (Figure 2C).
iv. $d\theta/d\sigma_1 \ge 0$. Higher rates of sex within the initial population increase the cutoff, making it more likely that weakly selected, partially recessive mutations favor sex (see Figure 2).
v. $d\theta/dr = 0$. The cutoff does not depend on the recombination rate. Although the cutoff does not change, it is possible to show that the region in which sex is favored to the left of the cutoff expands in area for increasing recombination, while the region to the right of the cutoff decreases in area for increasing recombination (as seen in Figure 4). Thus, looser linkage makes it more likely that weakly selected, partially recessive mutations favor sex.

Next, let us consider the stability criterion for three cases of special interest. First, when selection is weak, the governing eigenvalue becomes

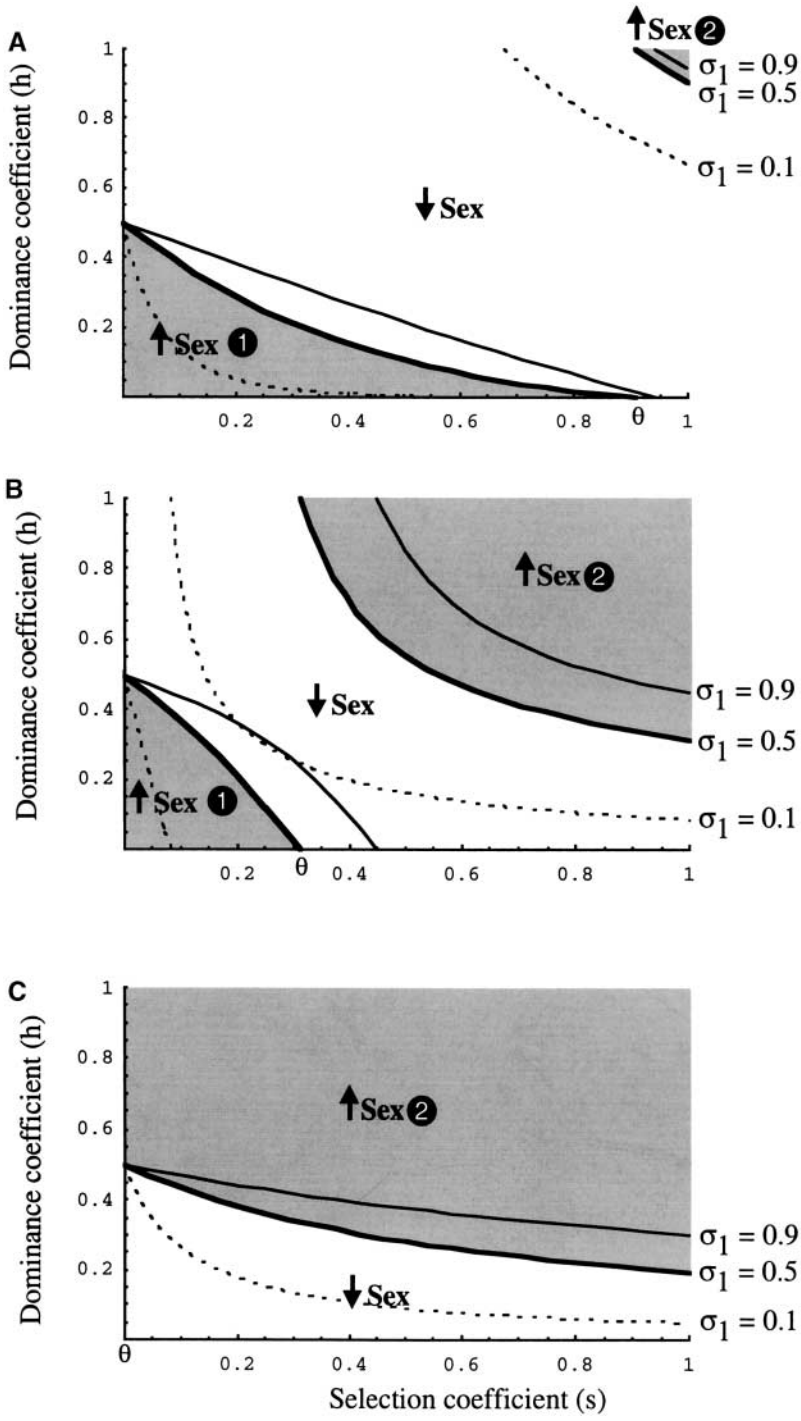

FIGURE 2.—Conditions under which a modifier that changes the frequency of sex spreads within an inbreeding population. In A, the modifier is recessive ($\sigma_2 = \sigma_1$; $\sigma_3 = \sigma_1 + 0.01$); in B, the modifier is additive ($\sigma_2 = \sigma_1 + 0.005$; $\sigma_3 = \sigma_1 + 0.01$); in C, the modifier is dominant ($\sigma_2 = \sigma_1 + 0.01$; $\sigma_3 = \sigma_2$). When sexual and asexual reproduction are equally frequent ($\sigma_1 = 0.5$), increased sex is favored within the shaded areas. Typically, there are two regions in which a modifier that increases the frequency of sex spreads: (1) Deleterious mutations are weakly selected and partially recessive and (2) deleterious mutations are strongly selected and partially dominant. The boundary between the two regions (θ) is indicated on the *x*-axis for $\sigma_1 = 0.5$. These regions shift to the left in less sexual populations ($\sigma_1 = 0.1$; dashed curves) and shift to the right in more sexual populations ($\sigma_1 = 0.9$; thin solid curves). Increasing the modifier's level of dominance contracts the first region and expands the second region, to the point that the first region entirely disappears when the modifier is completely dominant (C). Other parameters are $f = 0.05$, $r = 0.5$.

$$\lambda_{s\ll 1} = 1 + \mu\,\frac{f(1-f)\,(1-2h)(\sigma_3-\sigma_2)}{(f+(1-f)h)(f\sigma_2+(1-f)\sigma_3)} + O(\mu s, \mu^2). \quad (14)$$

Thus, for weak selection, a modifier allele that increases allocation to sexual reproduction spreads whenever deleterious mutations are partially recessive ($0 \le h < \frac{1}{2}$), as long as the rare modifier is not fully dominant. Second, when sexual reproduction involves high levels of selfing (f near 1), the governing eigenvalue becomes

$$\lambda_{f\sim 1} = 1 + \mu\frac{hs\,(\sigma_3-\sigma_1)}{(1-(1-hs)(1-\sigma_1))(1-(1-hs)(1-\sigma_3))} + O(\mu(1-f), \mu^2). \quad (15)$$

Thus, a rare modifier allele that causes more sex ($\sigma_3 - \sigma_1 > 0$) is always able to invade if inbreeding is high enough among the individuals that reproduce sexually (barring $h = 0$). Third, if the modifier introduces a small amount of sex ($\Delta\sigma \ll 1$) into a fully asexual population, the governing eigenvalue becomes

$$\lambda_{\sigma_1=0} = 1 + \mu\frac{f\sigma_2\sigma_3}{hs(f\sigma_2+(1-f)\sigma_3)} + O(\mu^2, \Delta\sigma^2). \quad (16)$$

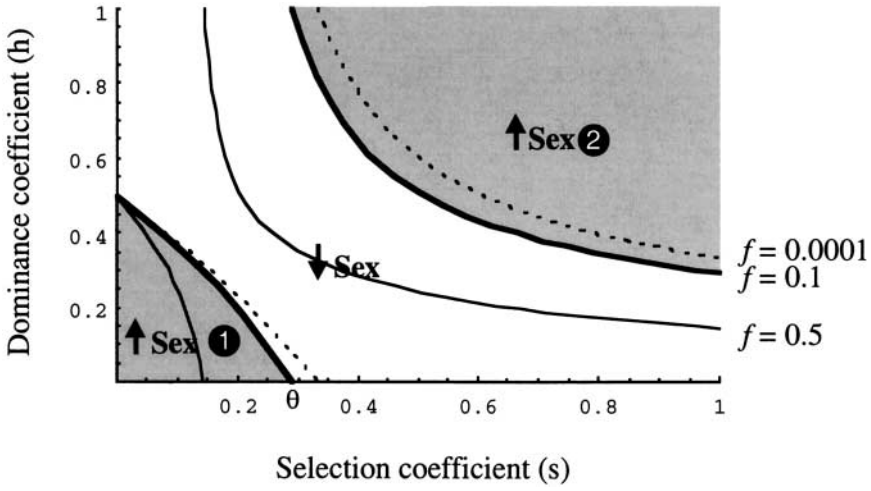

FIGURE 3.—The effect of the inbreeding rate on the conditions under which a modifier of sex spreads. The two regions in which sex is favored are shaded for intermediate inbreeding levels ($f = 0.1$), with their boundary occurring at θ. These regions shift to the right in less inbred populations ($f = 0.0001$; dashed curves) and shift to the left in more inbred populations ($f = 0.5$; thin solid curves). The regions in which sex is favored depend only weakly on f, unless inbreeding is common. While the curves are drawn using Equation 12, which assumes that $f \gg \mu$, nearly identical curves are generated by exact numerical calculations of the eigenvalues with $\mu = 10^{-6}$. Other parameters are $\sigma_1 = 0.5$, $\sigma_2 = \sigma_1 + 0.005$, $\sigma_3 = \sigma_1 + 0.01$, and $r = 0.5$.

Thus, a weak modifier allele is always able to invade an asexual population (barring $h = 0$). Strong modifiers that cause a substantial amount of sex within an otherwise asexual population spread, however, only if dominance (h) is sufficiently high.

Although the above analysis assumes gametophytic selfing, UYENOYAMA and BENGTSSON (1989) obtained similar results assuming sporophytic selfing and lethal mutations ($s = 1$). In the absence of selection, sporophytic selfing at rate b generates an inbreeding coefficient of $F = b/(2 - b)$ (UYENOYAMA and BENGTSSON 1989), while gametophytic selfing at rate f results in $F = f$. Thus, to compare the two forms of selfing, I set $f = b/(2 - b)$. Both Equation 12 and their results indicate that, when $s = 1$, sex is favored as long as h is greater than a threshold value (see right-hand edge of Figures 2–4). This threshold value differs quantitatively but not qualitatively between the two analyses.

In contrast to the case where inbreeding was absent, these results indicate that modifiers that increase the frequency of sex are positively selected when inbreeding is present for the most biologically relevant case of weak selection and partial recessivity of deleterious mutations, as long as a rare modifier is not fully dominant.

Simulation check: Deterministic simulations of the recursions were run using *Mathematica 3.0* (WOLFRAM 1991) to confirm that the above stability analyses correctly identified the conditions under which sex is favored. The parameters chosen were identical to those in Figures 1 and 2, with h and s set to every combination of {0.01, 0.1, 0.2, 0.3, . . . , 0.8, 0.9, 1.0} and with $\mu = 10^{-6}$. The frequencies of *AA*, *Aa*, and *aa* genotypes were set to the mutation-selection balance described by (7). The frequencies of *MM*, *Mm*, and *mm* genotypes were set to $p_M^2(1 - f) + fp_M$, $2p_Mp_m(1 - f)$, and $p_m^2(1 - f) + fp_m$, respectively, with the frequency of allele m ($p_m = 1 - p_M$) set to 0.001 and the selfing rate (f) set to 0 (for Figure 1) or 0.05 (for Figure 2). Linkage disequilibrium between the M and A loci was initially set to zero. The simulations were run for 10,000 generations with $f = 0$ and for 1000 generations with $f = 0.05$, and the total change in the modifier frequency was scored. For every parameter combination examined except four cases where no appreciable change in modifier frequency occurred (all near the curves with $F = 0$), the modifier rose in frequency when predicted by the regions delimited in Figures 1 and 2.

Evolutionary stable strategy: We turn now to the long-

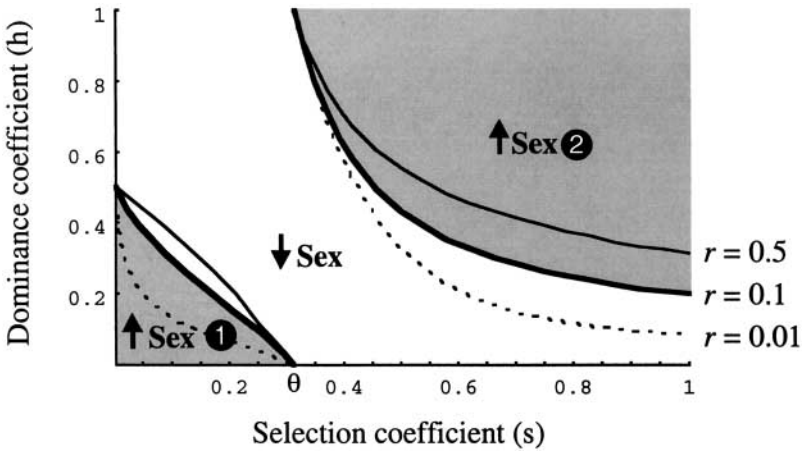

FIGURE 4.—The effect of recombination on the conditions under which a modifier of sex spreads within an inbreeding population. The two regions in which sex is favored are shaded for an intermediate recombination rate between the modifier and selected loci ($r = 0.1$). Region 1 contracts and region 2 expands when the loci are more tightly linked ($r = 0.01$; dashed curves), and the converse is observed for looser linkage ($r = 0.5$; thin solid curves). Other parameters are $\sigma_1 = 0.5$, $\sigma_2 = \sigma_1 + 0.005$, $\sigma_3 = \sigma_1 + 0.01$, and $f = 0.05$.

term evolution of the system and ask whether there is a level of sex at which the population will remain and be stable to invasion by any new allele that arises and modifies the frequency of sex. This level of sex represents an evolutionary stable strategy (ESS; Maynard Smith 1982). Because the strength of selection acting on the modifier is negligibly weak in the absence of inbreeding, we focus only on the case with inbreeding (analysis without inbreeding is available upon request).

When inbreeding is present, we must determine whether a value of σ_1 exists (σ_1^*) that cannot be invaded by any modifier allele causing the frequency of sex to change to σ_2 in heterozygotes and σ_3 in homozygotes from the eigenvalue (12). Let us begin with the border solutions ($\sigma_1^* = 0$ or 1). From (16), an asexual population ($\sigma_1^* = 0$) can be invaded by modifiers that introduce sex at sufficiently low rates. Thus, a fully asexual population is never an ESS. A population that is fully sexual ($\sigma_1^* = 1$) is stable to invasion by any weak modifier allele when inbreeding is common, specifically, when

$$f > [d_3hs + r(1 - hs)(2d_3 - (1 - 2h)s) + s\sqrt{h^2 - 2hr(1 - hs)(d_3 - 2(1 - h)^2s) + r^2(1 - 2h)^2(1 - hs)^2}]/[2d_3r(1 - hs) + 2hs(1 - h)(1 - hs + s)], \quad (17)$$

as illustrated in Figure 5. Numerical analyses suggest that, if the above condition holds and weak modifiers are unable to invade, then strong modifiers (σ_2, $\sigma_3 \ll 1$) are also unable to invade.

Interestingly, full sexuality ($\sigma_1^* = 1$) is the only ESS with allele *M* fixed of this model with inbreeding. Any intermediate value of σ_1^* can always be invaded by some weak modifier if we allow all possible levels of dominance for the modifier. This can be shown by noting that an intermediate ESS must satisfy both

$$\left.\frac{d\lambda_{f>0}}{d\sigma_2}\right|_{\substack{\sigma_2=\sigma_1^* \\ \sigma_3=\sigma_1^*}} = 0 \quad \text{and} \quad \left.\frac{d\lambda_{f>0}}{d\sigma_3}\right|_{\substack{\sigma_2=\sigma_1^* \\ \sigma_3=\sigma_1^*}} = 0,$$

but these describe two different equations in one unknown (σ_1^*) that cannot be satisfied simultaneously. That this might be true can be gleaned from Figure 2. Consider the case where $f = 0.05$, $\sigma_1 = 0.9$, $r = \frac{1}{2}$, $s = 0.4$, and $h = 0.097$. This case falls on the solid line in Figure 2B, indicating that a weak additive modifier that increases or decreases sex cannot invade. Figure 2A indicates, however, that a weak recessive modifier that increases the frequency of sex could invade, and Figure 2C indicates that a weak dominant modifier that decreases the frequency of sex could invade. Given that there is no reason to believe that modifier alleles that alter the allocation to sexual and asexual reproduction would exhibit a particular dominance level, we conclude that there is no possible ESS in partially inbreeding populations with both sexual and asexual reproduction. Instead, we predict that the level of sexuality should fluctuate up and down over evolutionary time, depending on the exact sequence of modifier alleles that appear within the population. Nevertheless, the long-term average level of sexuality will depend on the selection parameters, and we can infer from the local stability analyses (see Figures 2–4) that sexual reproduction will

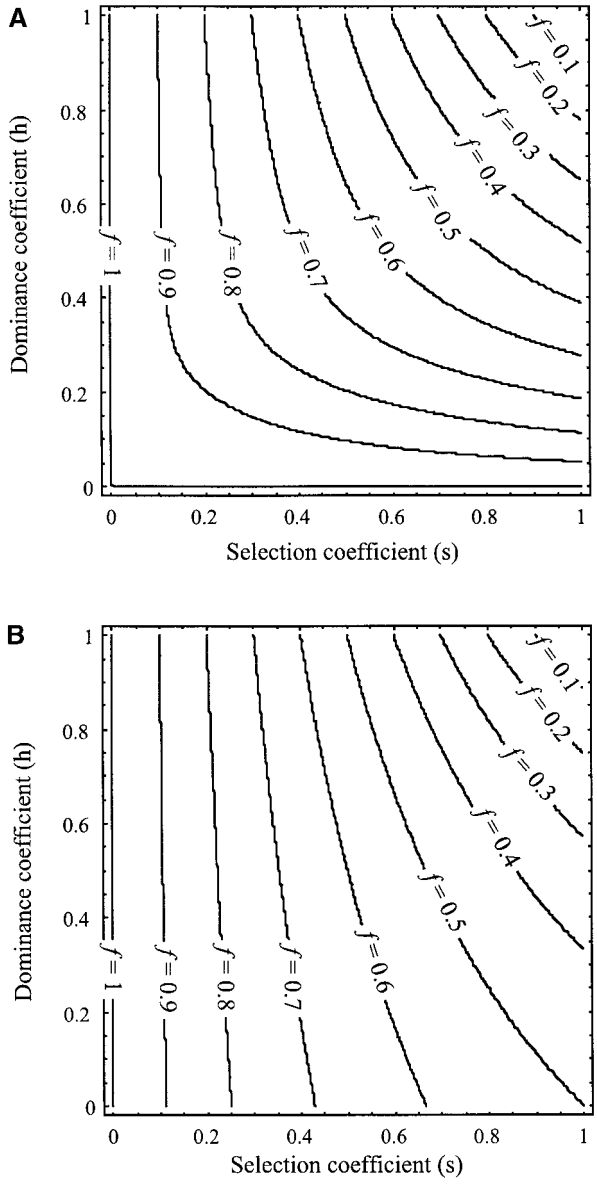

Figure 5.—The ESS level of sex with inbreeding. For a given level of inbreeding (f), complete sexuality ($\sigma_1^* = 1$) is an ESS when selection is sufficiently strong (to the right of the contours; Equation 17). For example, with $f = 1$, complete sexuality is an ESS over the entire parameter range, while, when $f = 0.1$, it is an ESS only in the last region at the top right of the graph. To the left of the contours there is no ESS, as there are always some combinations of σ_2 and σ_3 that allow a modifier to invade. A shows the case with free recombination between the modifier and fitness locus ($r = \frac{1}{2}$); B shows the case with complete linkage ($r = 0$).

be more common over evolutionary time when dominance (h) and selection coefficients (s) are both low or both high.

Genome-wide strength of selection: Here I estimate the genome-wide strength of selection acting on a modifier of sex assuming free recombination between all loci. Consider L fitness loci scattered throughout the genome, with no linkage disequilibrium between them, as might be expected if the fitness effects of each locus are independent and multiply together (Maynard Smith 1968; Eshel and Feldman 1970). The strength of indirect selection acting on a modifier allele through its effects on segregation at any one locus may be defined as $\phi \equiv \lambda - 1$, where λ is the leading eigenvalue. It can be shown that, if the modifier allele is rare and selection is weak, ϕ measures the asymptotic rate at which a modifier changes in frequency:

$$\phi \approx \frac{p_m' - p_m}{p_M p_m}.$$

Under the above assumptions, each fitness locus has only a small and independent effect on the frequency of the modifier, so we may sum the ϕ over the number of fitness loci (L) to get the genome-wide indirect effect of selection on a modifier of sex (Φ).

In the absence of inbreeding, the genome-wide indirect selection on a rare modifier is

$$\Phi_{f=0} = \sum_{i=1}^{L} -\mu^2(\sigma_2 - \sigma_1) \times \frac{(1 - 2h + h^2 s)(\sigma_2(1 - 2h + hs) - 2hs)}{h^2(s + \sigma_1(1 - s))(s + \sigma_2(1 - s))(2hs + \sigma_2(1 - hs))} + O(\mu^3) \quad (18a)$$

(from Equation 10). For each locus, the values of h, s, and μ will differ. Thus, this sum depends on the joint distribution of these parameters, which is unknown. Assuming, for the sake of argument, that there is little variance in each parameter and that selection is weak, the total strength of indirect selection on the modifier becomes

$$\Phi_{f=0} \approx -\bar{\mu} U(\sigma_2 - \sigma_1)\frac{(1 - 2\bar{h})^2}{2\bar{h}^2\sigma_1\sigma_2} + O(\bar{\mu}\,\bar{s}U, \bar{\mu}^2 U), \quad (18b)$$

where U is the mutation rate per diploid genome per generation ($U = 2L\bar{\mu}$) and a bar over a parameter denotes its average value. This genome-wide force selects against sex but is exceedingly weak (proportional to the per-locus mutation rate) unless mutations are very nearly recessive, such that the denominator in (18a) is on the order of $\bar{\mu}$.

Much stronger selection on the modifier is observed when inbreeding is present. For weak selection ($s \ll 1$; from Equation 14), the genome-wide selective force on a rare modifier is approximately

$$\Phi_{f>0;\, s\ll 1} = \sum_{i=1}^{L} (\lambda_{f>0} - 1) = U(\sigma_3 - \sigma_2)\frac{f(1 - f)(1 - 2\bar{h})}{2(f + (1 - f)\bar{h})(f\sigma_2 + (1 - f)\sigma_3)} + O(\bar{s}U, \bar{\mu}U). \quad (19a)$$

As long as the modifier is not completely dominant and as long as deleterious mutations are partially recessive ($0 \le \bar{h} < \frac{1}{2}$), weak selection against deleterious mutations favors the evolution of sex with a force that is proportional to the genome-wide mutation rate times the effect of the modifier ($\sigma_3 - \sigma_2$) times the inbreeding coefficient. The above calculations fail, however, to take into account the wide variation in dominance and selection coefficients among mutations. To make accurate predictions regarding the effects of segregation on the evolution of sex requires us to integrate over the joint distribution of h and s. Although this distribution is unknown, data from Drosophila suggest that a small percentage of deleterious mutations ($\sim$5%) are lethal, and these tend to be more highly recessive ($h \sim 0.02$–0.03) than mildly deleterious mutations (Simmons and Crow 1977; Charlesworth and Charlesworth 1999). Thus, it is worth asking whether the impact of relatively rare, lethal mutations outweighs the impact of mildly deleterious mutations on the evolution of sex. The genome-wide selective force on a modifier arising from such lethals can be simplified by assuming a weak additive modifier in Equation 12, yielding

$$\Phi_{f>0;s=1} = -U_{\text{lethal}}(\sigma_2 - \sigma_1) \times \frac{f((1 - f)(1 - h)\sigma_1 - h(1 + f))}{2(h + (1 - h)\sigma_1)(h + (1 - h)f\sigma_1)} + O(\Delta\sigma^2 U_{\text{lethal}}, \bar{\mu}_{\text{lethal}} U_{\text{lethal}}). \quad (19b)$$

Except in populations with very little sex (σ_1 small), lethal mutations that are highly recessive tend to select against sex, but given that lethals account for only a fraction of deleterious mutations, (19b) tends to represent a smaller selective force than (19a) does. For example, if $\sigma_1 = 0.5$, $f = 0.05$, $h = 0.1$ for weakly deleterious mutations, $h = 0.02$ for lethal deleterious mutations, and U_{lethal} is 5% of the total deleterious mutation rate, the strength of selection acting on a modifier arising from lethal mutations is only 10% of that arising from weakly deleterious mutations. Thus the combined force of many mild deleterious mutations and few lethal mutations still tends to favor the evolution of sex.

The above discussion assumes that sex entails no direct fitness costs (*e.g.*, costs associated with searching for and courting mates, producing males, etc.). We can incorporate such fitness costs, δ, by multiplying the terms in Equations 6 representing sexual reproduction by $(1 - \delta)$ and renormalizing. To simplify the analysis, I repeated the local stability analysis assuming a weak modifier and weak selection against deleterious muta-

tions. Modifier alleles now change in frequency in response to two forces: the direct costs of sex (measured by Ψ) and the indirect effects of altering segregation patterns at selected loci (measured by ϕ per locus and Φ per genome). Only if the net effect is positive ($\Psi + \Phi > 0$) will a modifier allele spread. To determine Ψ, the local stability analysis was performed by fixing the A allele at the selected locus (*i.e.*, by setting $\mu = 0$) and by defining $\Psi \equiv \lambda - 1$, yielding

$$\Psi = -\frac{\delta((1-f)(\sigma_2-\sigma_1) + f(\sigma_3-\sigma_1))}{1-\delta\sigma_1}, \quad (20)$$

which is negative for a modifier that increases the frequency of sex. Equation 20 equals the difference between the cost of sex paid by the old and new modifier alleles and is small whenever the modifier only slightly alters the frequency of sex. Next, mutations were reincorporated into the model, and a stability analysis was performed near the mutation-selection equilibrium. The indirect effect of the modifier per locus was defined as $\phi \equiv \lambda - 1 - \Psi$, which was summed across loci to get the net indirect effect of the modifier, Φ, again ignoring variation in the parameters. In the absence of inbreeding ($f = 0$), Φ is only on the order of the per-locus mutation rate and hence is negligible relative to the costs of sex. With inbreeding, however, the indirect selective force on a modifier is

$$\Phi_{\delta>0;s\ll1} = U\frac{1+\delta}{1-\delta}(\sigma_3-\sigma_2)\frac{f(1-f)(1-2\bar{h})}{2(f+(1-f)\bar{h})\sigma_1} + O(\bar{s}U, \Delta\sigma^2 U, \bar{\mu}U), \quad (21)$$

which differs slightly from (19a) because of the assumption of a weak modifier (reflected in the σ_1 term) and because the cost of sex reduces the efficacy of sexual reproduction in breaking down genetic associations [reflected in the $(1+\delta)/(1-\delta)$ term]. Overall, the effects of a modifier on segregation will overwhelm the costs of sex only if the sum of (20) and (21) is positive. For a modifier that increases the frequency of sex, this requires that mutations be partially recessive ($0 \le h < \frac{1}{2}$) and

$$U > \frac{2\sigma_1\delta(1-\delta)((1-f)(\sigma_2-\sigma_1)+f(\sigma_3-\sigma_1))(f+(1-f)h)}{(1-\delta\sigma_1)(1+\delta)(\sigma_3-\sigma_2)f(1-f)(1-2h).} \quad (22)$$

Condition (22) indicates that a modifier that causes a slight increase in the frequency of sex can invade despite a twofold cost of sex ($\delta = \frac{1}{2}$) as long as the genome-wide deleterious mutation rate (U) is high enough and/or the frequency of sex (σ_1) is initially low enough. As an example, when $f = 0.05$ and $h = 0.1$, the current allocation to sexual reproduction must be $< \sim 54\%$ if $U = 1$ or 7% if $U = 0.1$ for sex to evolve. These calculations indicate that the advantages of segregation can be strong enough within inbreeding populations to select for costly sex, especially when sex is currently rare. Counterintuitively, the cost of sex does not always make condition (22) harder to satisfy. This is because the cost of sex reduces the effective level of genetic mixing within a population, causing the initial population to be similar to a more asexual population in which the advantages of sex are greater. The above assumes, however, that the modifier is weak, so that the modifier alleles differ very little in the cost of sex imposed upon them; numerical examples suggest that the costs of sex are less likely to be counterbalanced by the benefits of segregation for modifier alleles that cause large increases in the frequency of sex. The above also assumes that selection at the fitness loci (s) is weak. With stronger selection, both the intrinsic costs of sex and the effects of sex on segregation can select against modifiers that increase the frequency of sex (see Figures 2–4). Nevertheless, this analysis indicates that the inclusion of substantial costs of sex is not fatal to the hypothesis that the consequences of segregation might have shaped the evolution and maintenance of sex.

Directional selection: *Quasi-linkage equilibrium (QLE):* Segregation could also provide an advantage to sex when populations are adapting to new environments. Insight into the dynamics of nonequilibrium populations can be gained using a method introduced by Kimura (1965), known as a quasi-linkage equilibrium (QLE) analysis (see Barton and Turelli 1991). The critical assumption made in a QLE analysis is that genetic associations reach an approximate balance between the forces that generate associations (*e.g.*, selection, drift, and inbreeding) and those that break them down (*e.g.*, sex and recombination) as long as the forces breaking down associations are sufficiently strong. Under this condition, genetic associations rapidly reach quasi-equilibrium at every point along the allele frequency trajectory. To solve for the QLE level of association, one sets the change in each association to zero and solves for its quasi-equilibrium value as a function of the current allele frequencies. Throughout the following I use the central-moment association measures as defined in Barton and Turelli (1991) and Kirkpatrick *et al.* (2002). These describe the gametic-phase linkage disequilibrium ($D = y_1y_4 - y_2y_3$), the linkage disequilibrium between alleles on homologous chromosomes, the departure from Hardy-Weinberg at locus **A** (the numerator of F in Equation 1), the departure from Hardy-Weinberg at locus **M**, the association between a modifier allele and the departure from Hardy-Weinberg at the viability locus, the association between a viability allele and the departure from Hardy-Weinberg at the modifier locus, and the association between the departure from Hardy-Weinberg at the modifier locus and the departure from Hardy-Weinberg at the viability locus. These seven association measures, along with the frequencies of the A and m alleles (p_A and p_m, respectively), provide nine independent equations that completely describe the dynamics and can be used to replace the genotypic frequencies, x_{ij}, in Equations 6.

QLE without inbreeding: To find the QLE without inbreeding ($f = 0$), it was assumed that selection is weak [$s = O(\xi)$] and that the modifier is weak [$\sigma_2 = \sigma_1 + O(\xi)$ and $\sigma_3 = \sigma_1 + O(\xi)$], where ξ is some small term ($\xi \ll 1$). The QLE values for each association measure were solved, keeping terms up to $O(\xi^2)$, and then used to determine the change in frequency of the modifier allele ($\Delta p_m = p'_m - p_m$). The resulting equation for the per-generation change in the modifier is

$$\Delta p_m = -s^2 p_M p_m \frac{\partial\sigma}{\sigma_1^2}(1 - 2h)^2(p_A p_a)^2 + O(\xi^4), \qquad (23)$$

where

$$\partial\sigma = (\sigma_2 - \sigma_1)p_M + (\sigma_3 - \sigma_2)(1 - p_M).$$

(The derivation of Equation 23 assumes that h is not very near ½. For nearly additive beneficial alleles, see Equation 31.) Equation 23 indicates that, under weak selection, modifiers that increase the frequency of sex are always selected against. To leading order in s, Equation 23 is identical to the per-generation change in the modifier expected at mutation-selection balance ($1 - \lambda_{f=0}$ from Equation 10) under the combined set of assumptions: The modifier is weak, m is rare, and p_A is near the equilibrium described by Equation 7. Thus, under directional selection as well as at a mutation-selection balance, weak selection on locus **A** generates indirect selection against a modifier allele that increases allocation to sexual reproduction as long as inbreeding is absent.

How strong is this force? As the A allele rises in frequency from $p_{A,0}$ at time 0 to $p_{A,T}$ at time T, the cumulative change in the modifier allele would be

$$\Delta p_{m,\text{total}} \approx \int_{t=0}^{T} -s^2 p_M p_m \frac{\partial\sigma}{\sigma_1^2}(1 - 2h)^2(p_A p_a)^2 dt. \qquad (24)$$

Under the assumptions of weak selection and frequent sexual reproduction, we may approximate the per-generation change in p_A by the differential equation

$$\frac{dp_A}{dt} \approx p'_A - p_A \approx s p_A p_a g(p_A), \qquad (25)$$

where

$$g(p_A) = (1 - h)(1 - p_A) + h p_A.$$

Transforming the independent variable in Equation 24 from time (t) to allele frequency (p_A), using Equation 25 and integrating, we get

$$\Delta p_{m,\text{total}} \approx -s p_M p_m \frac{\partial\sigma}{\sigma_1^2} \times \left(\frac{(p_{A,T} - p_{A,0})(2h + (p_{A,T} + p_{A,0})(1 - 2h))}{2} - \frac{h(1 - h)}{(1 - 2h)} \operatorname{Log}\left[\frac{g(p_{A,0})}{g(p_{A,T})}\right] \right). \qquad (26a)$$

If the beneficial allele rises from a low initial frequency ($p_{A,0}$ near 0) to a high final frequency ($p_{A,T}$ near 1), the above simplifies to

$$\Delta p_{m,\text{total}} \approx -s p_M p_m \frac{\partial\sigma}{\sigma_1^2}\left\{\frac{1}{2} - \frac{h(1 - h)}{(1 - 2h)} \operatorname{Log}\left[\frac{1 - h}{h}\right]\right\}. \qquad (26b)$$

The factor in braces is nearly quadratic in shape and falls from ½ at $h = 0$ to 0 at $h = ½$ and then rises back to ½ at $h = 1$. Thus, the total strength of selection on the modifier ($s_{m,\text{total}} = \Delta p_{m,\text{total}}/(p_M p_m)$) arising per selective sweep is $< -\partial\sigma s/(2\sigma_1^2)$ when inbreeding is absent. Consequently, the total amount of selection acting on the modifier locus **M** amounts to less than one generation's worth of selection on locus **A**, unless sex is rare. Note, however, that the QLE approximation will break down if sex is so rare that selection builds genetic associations faster than sex breaks them down.

QLE with inbreeding: A similar QLE analysis was conducted assuming that sexual reproduction occurs with inbreeding. The following equations for the change in the frequency of the modifier must be added to the above QLE results without inbreeding. Unless inbreeding levels are low [$O(\xi)$ or smaller], however, inbreeding causes a greater change in the modifier and so the previous terms may be neglected. Per generation, the modifier allele changes in frequency by

$$\Delta p_m = s p_M p_m \frac{\nabla\sigma}{\sigma_1}(1 - 2h)f(1 - f)p_A p_a + O(\xi^3), \qquad (27)$$

where

$$\nabla\sigma = (\sigma_2 - \sigma_1)(1 - p_M) + (\sigma_3 - \sigma_2)p_M.$$

For this QLE approximation to be valid, sex must be frequent relative to the rate of inbreeding ($\sigma_1 \gg f$); otherwise the genetic associations are slow to reach steady state. Equation 27 indicates that a directional modifier allele that increases the frequency of sex will spread whenever $h < ½$ under weak selection. Again, to leading order in s, Equation 27 is identical to the per generation change in the modifier expected at mutation-selection balance ($1 - \lambda_{f>0}$ from Equation 12) under the combined set of assumptions. There is, however, a key biological difference: The requirement that h be $<½$ implies that deleterious mutations must be partially *recessive* but beneficial mutations must be partially *dominant* for sex to be favored.

Equation 27 may be integrated over a selective sweep using Equation 25 to rewrite time in terms of the allele frequency, p_A, where now $g(p_A) = (1 - f)((1 - h)(1 - p_A) + h p_A) + f$. The total change in the modifier per generation is then

$$\Delta p_{m,\text{total}} \approx p_M p_m \frac{\nabla\sigma}{\sigma_1} f \operatorname{Log}\left[\frac{g(p_{A,0})}{g(p_{A,T})}\right]. \qquad (28)$$

For a directional modifier that increases the frequency of sex, Equation 28 is positive at $h = 0$, declines with increasing h, reaches 0 at $h = ½$, and becomes negative

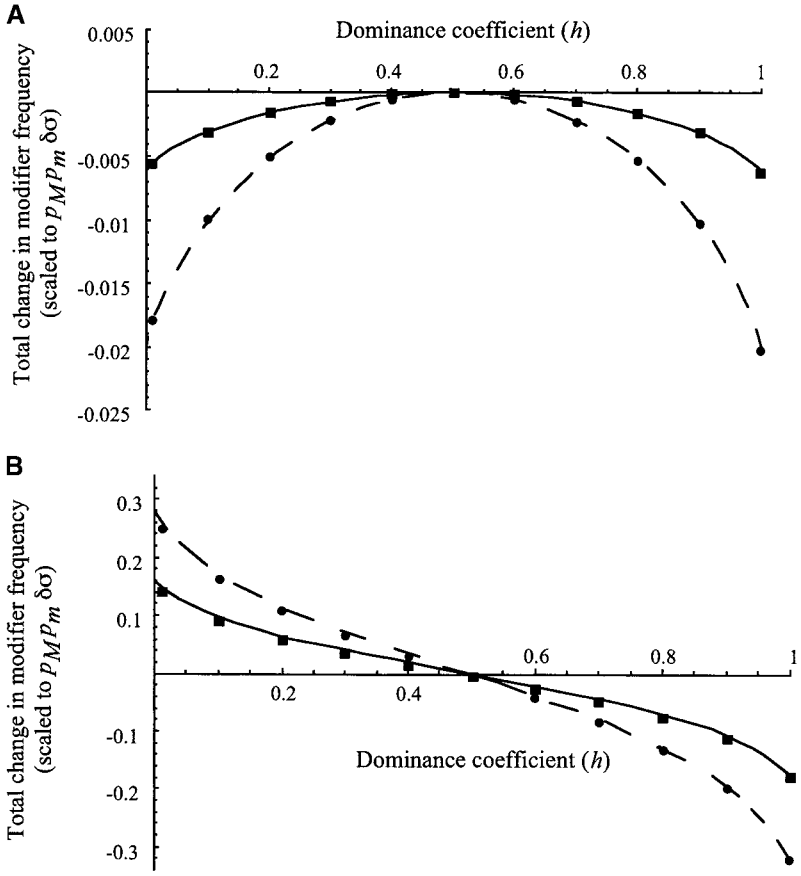

FIGURE 6.—The total change in frequency of a modifier allele that increases allocation to sexual reproduction over the course of a selective sweep. The plots scale the total change as $\Delta p_{m,\text{total}}/(p_M p_m \delta\sigma)$, which represents the selection gradient acting on the modifier, assuming a weak additive modifier ($\sigma_3 = \sigma_1 + 2\delta\sigma$). A is without inbreeding ($f = 0$; using Equation 26a); B is with inbreeding ($f = 0.05$; using the sum of Equations 26a and 28). The long dashed curves are the analytical results and the circles are the simulation results when sexual and asexual reproduction are equally frequent ($\sigma_1 = 0.5$). The solid curves are the analytical results, and the squares are the simulation results when sex is initially common ($\sigma_1 = 0.9$). Other parameters are $\sigma_2 = \sigma_1 + 0.005$, $\sigma_3 = \sigma_1 + 0.01$, $r = 0.5$, $p_{A,0} = 0.001$, $p_{A,T} = 0.999$, $p_{M,0} = 0.999$, and $s = 0.01$. As selection becomes stronger, the analytical results become less accurate.

for $h > \frac{1}{2}$. In the case where the beneficial allele rises from a low initial frequency ($p_{A,0}$ near 0) to a high final frequency ($p_{A,T}$ near 1), (28) becomes approximately

$$\Delta p_{m,\text{total}} \approx 2p_M p_m \frac{\nabla\sigma}{\sigma_1} \frac{f(1-f)}{1+f}(1-2h), \qquad (29)$$

where the approximation works best near $h = \frac{1}{2}$ and underestimates the change in the modifier for h near zero or one. Equations 28 and 29 indicate that each selective sweep within a genome causes a modifier allele that promotes sexual reproduction to rise in frequency, as long as beneficial alleles are weakly selected and partially dominant. Now the total amount of selection acting on the modifier depends not on s but on f and will be substantial when inbreeding rates are high.

Simulation check: The above QLE predictions were compared to deterministic simulations, which were performed as described for the case of a mutation-selection balance with the following exceptions. The *A* allele started at a frequency of 0.001, and the simulations were run until *A* reached a frequency of 0.999. Mutations were ignored. The initial frequencies of *AA*, *Aa*, and *aa* genotypes were set to $p_A^2(1-f) + fp_A$, $2p_Ap_a(1-f)$, and $p_a^2(1-f) + fp_a$, respectively. Finally, weak selection ($s = 0.01$) and high initial frequencies of sex ($\sigma_1 = 0.5$ or 0.9) were assumed, as required for the QLE analysis to be valid. Figure 6 illustrates that the QLE analysis accurately predicts the total change in the modifier observed in simulations. Further simulations (available upon request) demonstrate, however, that the QLE predictions can be off by as much as a factor of five if either s or σ_1 is set to 0.1.

As noted after Equations 23 and 27, the QLE results with directional selection are equivalent to those obtained at a mutation-selection balance when selection is assumed to be weak. Simulations were performed to explore whether the results remain similar under stronger selection. Without inbreeding, simulations indicate that the answer is "yes" (Figure 7A). With inbreeding, however, the conditions that favor sex at mutation-selection balance and under directional selection differ, especially as selection becomes stronger (Figure 7B). The discrepancy diminishes when the simulations are allowed to run for longer while the *a* allele is rare, as is the case at mutation-selection balance. Nevertheless, the qualitative result remains that sex, with inbreeding, is favored when dominance levels are low and selection is weak or when dominance levels are high and selection is strong.

COMPARISONS TO OTHER MODELS AND INTERPRETATION

The results derived above demonstrate that selection acts on a modifier of sex in complex ways. Some intuitive insight into the results can be gained by drawing paral-

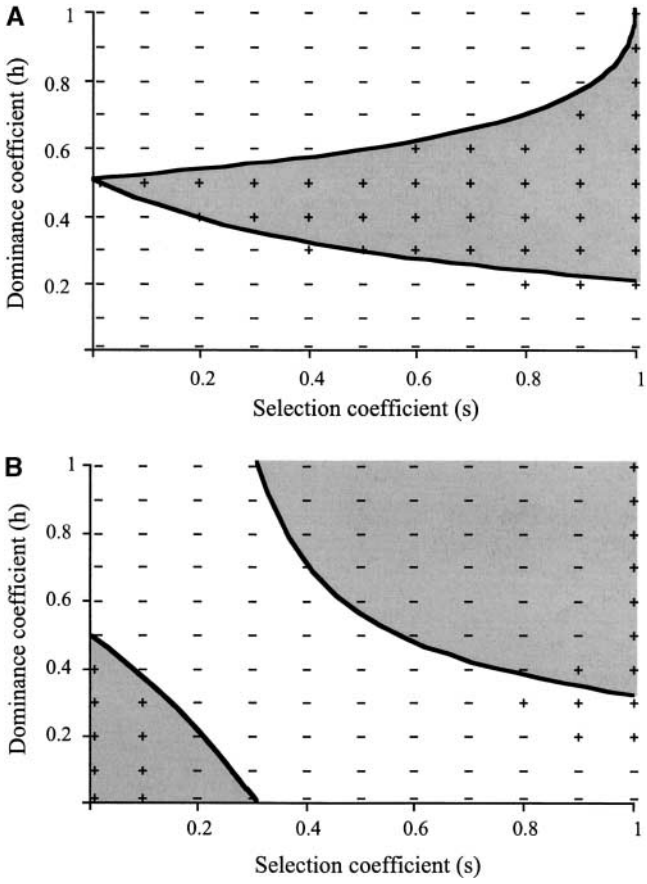

FIGURE 7.—Conditions under which a modifier allele that promotes sexual reproduction increased in frequency over the course of a selective sweep. Such conditions are denoted by a "+"; a "−" indicates that the modifier decreased in frequency over the course of the simulations. The simulations of a selective sweep are compared to the conditions under which sex is favored at a mutation-selection balance (shaded regions), on the basis of Equation 11 when inbreeding is absent ($f = 0$; A) and on the basis of Equation 12 when inbreeding is present ($f = 0.05$; B). Other parameters are $\sigma_1 = 0.5$, $\sigma_2 = \sigma_1 + 0.005$, $\sigma_3 = \sigma_1 + 0.01$, $r = 0.5$, $p_{A,0} = 0.001$, $p_{A,T} = 0.999$, $p_{M,0} = 0.999$, $F_{A,0} = f$, and $F_{M,0} = f$.

lels to other modifier models. In particular, the evolution of segregation in response to one-locus genetic associations is very similar to the evolution of recombination in response to linkage disequilibrium. In both cases, fitness interactions play a key role. With respect to modifier evolution, these fitness interactions are naturally measured by ι in the one-locus case (see Equation 8) and by epistasis in the two-locus case [with haploid selection, $\varepsilon = \text{Fitness}(AB)\text{Fitness}(ab) - \text{Fitness}(Ab)\text{Fitness}(aB)$; see, *e.g.*, BARTON 1995; BERGMAN *et al.* 1995]. In both cases, negative fitness interactions ($\iota < 0$ or $\varepsilon < 0$) generate negative genetic associations ($F < 0$ or $D < 0$, respectively; Equation 8; ESHEL and FELDMAN 1970), which reduce genetic variation and impede selection. With no other force generating associations besides selection, genetic mixing (sex and recombination) breaks down the harmful genetic associations created by negative fitness interactions. Consequently, mean fitness at equilibrium is higher in sexual populations than in asexual populations when fitness interactions are negative (KONDRASHOV 1982; CHASNOV 2000).

Even when higher rates of genetic mixing would increase equilibrium mean fitness, increased levels of genetic mixing will not necessarily evolve, as shown by modifier models. In the absence of selfing and other forms of inbreeding, Equation 11 must hold for the advantages of segregation to favor the evolution of higher frequencies of sex. That is, the one-locus measure of fitness interactions, ι, must be negative (below the topmost curve in Figure 1) but weak (above the bottom curves in Figure 1). In a model of a fully sexual population in which directional selection acts and in which modifier alleles alter recombination rates between fitness loci, a similar condition must be met by the two-locus measure of fitness interactions, ε, for the evolution of higher rates of recombination (BARTON 1995). Specifically, epistasis must satisfy

$$-a_A a_B\left(\frac{1 - r_{MA}}{r_{MA}} + \frac{1 - r_{MB}}{r_{MB}} + 1\right) < \varepsilon < 0, \qquad (30)$$

where a_A and a_B are the additive effects of selected alleles at two fitness loci, **A** and **B**, which are located at distances r_{MA} and r_{MB}, respectively, from a modifier locus (BARTON 1995; see Equation 12 in LENORMAND and OTTO 2000). This condition can be interpreted as follows (see BARTON 1995; BARTON and CHARLESWORTH 1998; OTTO and MICHALAKIS 1998; OTTO and LENORMAND 2002). Whenever genetic associations become negative ($D < 0$) as a result of negative fitness interactions ($\varepsilon < 0$), a modifier allele that increases recombination increases the production of the most extreme genotypes, which are underrepresented within the population (*AB* and *ab* in the model of recombination). Because this increases the genetic variance in fitness and, hence, the efficacy of directional selection, the modifier allele, over the long term, becomes associated with the fittest alleles at loci **A** and **B**. The first two terms in the parentheses of (30) measure the persistence time of these beneficial associations, where $(1 - r_{ij})/r_{ij}$ is the expected number of generations into the future that a modifier allele will remain associated with a viability allele with which it is currently found. The last term (+1) in the parentheses arises from the short-term effect of recombination on fitness (the "recombination load"), which is disadvantageous except when $-a_A a_B < \varepsilon < 0$, because recombination breaks apart genetic associations that have been favored and built by selection. Thus, a modifier that increases recombination will spread within a population when epistasis is sufficiently weak and recombination rates are sufficiently low that the long-term benefits of recombination causing modifiers to become associated with fit alleles outweigh any short-term disadvantages.

We can rewrite the invasion criterion (11) in a form similar to (30) by defining fitnesses in an analogous man-

ner, with $(1 - hs) = (1 - a_A)$ and $(1 - s) = (1 - a_A)^2 + \iota$. To leading order in selection, (11) then becomes

$$-a_A^2\left(\frac{1 - \sigma_2 r_{MA}}{\sigma_2 r_{MA}} + \frac{1 - \sigma_2/2}{\sigma_2/2} + 1\right) < \iota < 0. \quad (31)$$

Although the first two terms in the parentheses look different from (30), they measure the very same quantity: the expected persistence time of associations between a modifier allele and the fittest viability alleles. Now, the first term describes the expected persistence time for modifier and viability alleles initially on the same chromosome, whereas the second term describes the persistence time for modifier and viability alleles initially on homologous chromosomes (see the appendix). Hence, conditions (30) and (31) are formally equivalent. Furthermore, it can be shown that Equation 31 can also be obtained from a QLE analysis of directional selection when ι is assumed to be of order $(a_A)^2$, which implies that h is very nearly ½. (I am indebted to Thomas Lenormand for showing this.)

As with a modifier of recombination, a modifier of sex experiences the sum of two selective forces: (a) long-term selection resulting from changing the genetic variance in fitness and (b) short-term selection resulting from the immediate effects of a modifier allele on the mean fitness of offspring. Whenever one-locus genetic associations become negative ($F < 0$) as a result of negative fitness interactions ($\iota < 0$), a modifier allele that increases sex increases the production of the most extreme genotypes, which are underrepresented within the population (*AA* and *aa* genotypes in this model). Because this increases the genetic variance in fitness and, hence, the efficacy of directional selection over time, the modifier allele gains a long-term benefit by becoming associated with fitter alleles. When fitness interactions are very negative, however, the offspring with extreme genotypes generated by genetic mixing have very low fitness, on average, which selects against the modifier in the short term. Specifically, the extreme genotypes (*AA* and *aa*) are less fit, on average, than the intermediate genotype (*Aa*) whenever $h < ½$ (or $\iota + a_A^2 < 0$). Thus, only in a relatively small parameter range, $-a_A^2 < \iota < 0$, are there both long- and short-term benefits to increasing the frequency of sex. Otherwise, the short-term disadvantage (*i.e.*, the immediate reduction in the average fitness of offspring) counteracts the long-term benefit (*i.e.*, the genetic association with fitter alleles). Thus, even though the equilibrium mean fitness would be increased by having more sex whenever $\iota < 0$, a modifier that increases the amount of sex can spread within a population only when condition (31) is met. The above discussion focuses on negative fitness interactions because positive fitness interactions generate both a long- and short-term disadvantage to sex or recombination, and modifiers that increase the extent of genetic mixing never spread (above topmost curve in Figure 1). Note that both conditions (30) for the evolution of recombination and (31) for the evolution of sex indicate that selection more often favors the evolution of increased genetic mixing when rates of genetic mixing are initially low.

These conclusions assume, however, that genetic associations result only from fitness interactions. Population structure (Lenormand and Otto 2000), drift (Otto and Barton 2001), and nonrandom mating (Uyenoyama and Bengtsson 1989; this article) also generate genetic associations that affect the evolution of modifier alleles. In particular, inbreeding generates positive one-locus genetic associations ($F > 0$; Equation 9), where the extreme genotypes (*AA* and *aa*) are overrepresented. Understanding the evolution of a modifier of sex is particularly difficult in this case, however, because sex involves two processes: Random mating *breaks down* genetic associations but selfing/inbreeding *generates* genetic associations. In fact, the observation that there are two opposite regions in which sex is favored suggests that how a modifier acts may differ depending on the strength of selection. Clues to the underlying forces at work can be obtained by looking at how genetic associations accumulate over time. In a stability analysis, this can be accomplished by calculating the genetic associations along the eigenvector associated with the leading eigenvalue.

At mutation-selection balance, a numerical analysis of this eigenvector indicated that one and only one of the genetic association measures switches sign as the strength of selection (s) crosses the boundary (θ) between regions 1 and 2 (see Figures 2–4): the association between the modifier allele and homozygosity at the fitness locus. In region 1, a modifier allele that increases the frequency of sex is more often found among *heterozygotes* at the fitness locus; this implies that the modifier is causing a reduction in genetic variance at the fitness locus, which will reduce the efficacy of selection and provide a long-term disadvantage. Note, however, that heterozygotes are more fit, on average, whenever $h < ½$, in which case this very same association provides a short-term benefit to the modifier. Thus, in region 1, the modifier can spread when this short-term benefit is strong enough (h low enough) relative to the long-term disadvantage. In region 2, a modifier allele that increases the frequency of sex is more often found among *homozygotes* at the fitness locus; this indicates that the modifier is causing an increase in genetic variance at the fitness locus, increasing the efficacy of selection and providing a long-term advantage. These homozygotes are more fit, on average, whenever $h > ½$, in which case this genetic association provides a short-term benefit to the modifier. We would thus expect the modifier to spread in region 2 whenever h is high enough, as is observed (see region 2; top right in Figures 2–4). This story is overly simplified, however, and the other association measures do play a role, especially when

selection is near the boundary (θ) where the association between the modifier allele and homozygosity at the fitness locus becomes weak.

In summary, the existence of two regions in which sex is favored in the presence of inbreeding occurs because a modifier that causes more sex goes from decreasing the genetic variance to increasing the genetic variance as selection (s) becomes stronger. Why should selection play such a key role? The stronger selection is, the more rapidly genetic variance is depleted. With strong selection, lineages that have been asexual for longer will have exhausted more of the genetic variance in fitness and exhibit less homozygosity at the **A** locus. In such a population, a modifier that increases the frequency of sex with inbreeding will regenerate homozygosity, restoring this genetic variance. But why then would a modifier that increases the frequency of sex with inbreeding decrease homozygosity when selection is weak? I believe that the answer lies in the fact that unless it is dominant, a rare modifier allele causes more sex in homozygotes (mm) than in heterozygotes (Mm) ($\sigma_3 > \sigma_2$). When inbreeding is present, homozygotes at the modifier locus are more often homozygous at the fitness locus as well (a positive identity disequilibrium; Hartl and Clark 1989). Consequently, modifier alleles that increase the frequency of sex tend to act more strongly in homozygotes than in heterozygotes at the fitness locus, which causes, on average, a breakdown in homozygosity. This effect should become less pronounced as a modifier becomes more dominant. Indeed, a fully dominant modifier that increases the frequency of sex acts as strongly in heterozygotes as in homozygotes, and it never causes a net reduction in the frequency of homozygotes at the fitness locus. This helps explain why region 1 disappears for a rare dominant modifier ($\theta = 0$).

Interestingly, the results in region 2, where a modifier that increases the frequency of sex acts to increase the frequency of homozygotes, are reminiscent of results from life-cycle models, where a modifier alters the relative lengths of the haploid and diploid phases in an organism with an alternation of generations (Perrot *et al.* 1991; Otto and Goldstein 1992; Orr and Otto 1994; Otto 1994). In these models, expansion of the diploid phase is favored when dominance levels are low, because diploid individuals then mask deleterious alleles. Conversely, when dominance levels are high, expansion of the haploid phase is favored, because deleterious alleles are no longer masked in diploids and because selection is inherently more efficient in haploids in which the full fitness effects of mutations are felt. By noting that homozygous individuals in this model (Equation 2) have the same fitness as haploid individuals in the life-cycle models, inbreeding can be seen as a way in which haploid selection can be mimicked in diploids. Consequently, modifiers that increase the frequency of sex, when they act primarily to increase homozygosity, should be favored whenever haploidy is favored, *i.e.*, when dominance levels are high, as is observed in region 2. Indeed, the degree of dominance (h) above which sex is favored increases as a function of the recombination rate between modifier and fitness loci (Figure 4, top right) and as a function of the level of sex (Figure 2, top right) in a manner similar to that observed in life-cycle models (Otto and Goldstein 1992; Otto and Marks 1996).

DISCUSSION

Modifier models allow us to explore the directions in which reproductive systems are likely to evolve by tracking the fate of genes that alter reproduction. In this article, I have explored the evolution of a modifier that alters resource allocation to sexual *vs.* asexual reproduction. The fact that sexual reproduction entails the segregation of alleles at each diploid locus whereas asexual reproduction faithfully reproduces parental genotypes generates differences in the expected fitness of sexually produced and asexually produced offspring. Fitness differences among offspring were incorporated into the model by including loci that were directly subject to selection, either purifying or directional. Under purifying selection, it was assumed that the population had reached a mutation-selection balance. Under directional selection, it was assumed that a beneficial allele was rising toward fixation within the population. Both random mating and inbreeding among the sexually produced gametes were explored.

With random mating among gametes and weak selection at the fitness loci, modifier alleles that increase the frequency of sexual reproduction are selected against (Figures 1 and 7A). This result holds whether the fitness loci are subject to purifying or directional selection. With stronger selection at the fitness loci, sexual reproduction was favored, but only under a narrow range of dominance coefficients. Dominance had to be submultiplicative and yet not strongly so (see condition 11; Figures 1 and 7A). This result echoes the conditions on epistasis under which increased rates of recombination are favored (Barton 1995), indicating that the forces selecting for increased sex in this model of segregation and for increased recombination are fundamentally similar. Nevertheless, with random mating among sexually produced gametes, selection on a modifier of sex is very weak. Indeed, across a genome of loci held at mutation-selection balance, the selective force on the modifier is only proportional to the *per locus* mutation rate (Equation 18). Similarly, over all of the generations during which a beneficial allele rises in frequency, the selective force on the modifier is only proportional to one generation of selection on the beneficial allele itself. Thus, with random mating, the selective force acting on the modifier is negligibly weak and would almost certainly be offset by the direct fitness costs of sex (the cost of males,

the cost of searching for mates, the cost of remaining unfertilized, etc.).

With inbreeding among gametes, however, an entirely different picture emerges. In this article, inbreeding was modeled as gametophytic selfing, where gametes mate with identical gametes produced by a haploid parent in an organism that alternates between free-living haploid and diploid phases. Similar results were, however, obtained by Uyenoyama and Bengtsson (1989), assuming sporophytic selfing, where there is random mating among the gametes produced by a diploid individual, although these authors examined only lethal deleterious mutations ($s = 1$). I conjecture that any mating system that generates inbreeding, including localized mating in spatially structured populations, will behave in a similar fashion by generating excess homozygosity, but this conjecture remains to be verified. In the model of inbreeding explored here, modifier alleles that increase the frequency of sexual reproduction are favored when selection is weak at the fitness loci, as long as deleterious mutations are partially recessive or beneficial mutations are partially dominant ($h < \frac{1}{2}$; assuming that the modifier is not fully dominant). With stronger selection at the fitness loci, lower values of h are required for sex to be favored, until a threshold is reached (Equation 13), after which higher values of h select for sex. Thus, unexpectedly, there are two entirely opposite regions under which sex is favored: when deleterious alleles are partially recessive and selection is weak and when deleterious alleles are partially dominant and selection is strong (Figures 2–4 and 7B).

The behavior of the model is quite complex with inbreeding, however, and the results are sensitive to the dominance relationships among the modifier alleles. For example, if a new modifier allele is completely dominant and rare, then the first region disappears and only high dominance levels favor the evolution of sex (see Figure 2C). The fact that the behavior of the system is sensitive to the dominance of the modifier implies that a species will never reach an evolutionarily stable state with both sexual and asexual reproduction. That is, there will always be a modifier allele that can invade if it has the right dominance relationship to the current modifier allele. Indeed, the only ESS possible with inbreeding is that of full sexuality, but this ESS is stable over a large range of parameters (h and s) only when inbreeding levels are near one (Figure 5). Because the evolutionary transitions that can occur depend on the dominance of the modifier as well as the selection coefficients, we expect that reproductive systems should not follow a predictable evolutionary trajectory but should be labile over evolutionary time. Nevertheless, statements can be made about the long-term average level of sexuality: Higher levels of sex are expected, on average, when selection is weak and $h < \frac{1}{2}$ (as is commonly considered to be the case for newly arising deleterious mutations) or when selection is strong and $h > \frac{1}{2}$.

TABLE 3

Genome-wide selection gradient on a modifier of sex compared to a modifier of recombination

U	$\frac{\Phi}{\delta r}$ (Barton 1995)	$\frac{\Phi}{\delta\sigma}$ (this article)		
		$f = 0$	$f = 0.01$	$f = 0.05$
2.0	0.00271	−0.00015	0.01834	0.05451
1.5	0.00143	−0.00012	0.02150	0.06967
1.0	0.00056	−0.00009	0.02100	0.07119
0.5	0.00008	−0.00005	0.01567	0.05477
0.1	−0.00001	−0.00001	0.00481	0.01716

Table 3 of Barton (1995) lists the selection gradient on a modifier ($\Phi/\delta r$) that increases the recombination rate between *MM* and *mm* individuals by $2\delta r$ at a mutation-selection balance with deleterious mutation rate, U, per diploid genome per generation. Using Equations 18a and 19a, I compare these results to the selection gradient on a modifier of sex ($\Phi/\delta\sigma$), assuming a weak additive modifier ($\sigma_3 = \sigma_1 + 2\delta\sigma$). In both cases, nearly free recombination is assumed. In the Barton analysis, epistatic selection was assumed, and the fitness of an individual was given by $\bar{W} = \exp(-an - bn^2/2)$, where n is the number of heterozygous deleterious mutations and a and b are parameters measuring the strength of selection and epistasis. In this analysis, I assume multiplicative selection. To make the strength of selection on each new mutation comparable, I define $(1 - hs)^{\bar{n}} = \bar{W}$, where the average fitness ($\bar{W}$) and the average number of mutations carried by an individual ($\bar{n}$) are given in Table 3a of Barton (1995). Other parameters are $h = 0.1$, $\sigma_1 = 0.5$, and $\mu = 10^{-6}$.

Inbreeding, even at relatively low levels, generates much stronger selection on a modifier of sex than that observed in the absence of inbreeding. Across a genome of loci held at mutation-selection balance, the selective force on the modifier per generation is proportional to the *per genome* mutation rate and to the inbreeding coefficient (Equation 19). Indirect selection on a modifier that slightly increases the frequency of sex can even be strong enough to counteract a twofold cost of sex if the genome-wide mutation rate is sufficiently high (see Equation 21). To illustrate the strength of the evolutionary forces acting on the reproductive system, Table 3 compares selection on a modifier in this model to selection in Barton's (1995) model of recombination with epistasis (from his Table 3). For the parameters compared, sexual reproduction is favored much more strongly by the advantages of segregation assuming partially recessive deleterious mutations than by the advantages of recombination assuming negative epistatic fitness interactions, as long as sex involves inbreeding. The level of inbreeding required, however, is not strong and is consistent with levels of increased homozygosity generated by population structure in many organisms (McCauley and Eanes 1987; Berg and Hamrick 1997; Merilä and Crnokrak 2001). This comparison assumes that the strength of selection on each new muta-

tion is equal in the two models, that fitness effects across loci are multiplicative in the model of segregation (to minimize the effects of recombination in this case), and that fitness effects across loci are negatively epistatic in the model of recombination (to maximize the benefits of recombination). Of course, the model in this article could be expanded to incorporate epistatic interactions among fitness loci, in which case we would expect selection on a modifier of sex to arise from both the effects of segregation explored here and the effects of recombination explored by Barton (1995). In addition to generating a stronger evolutionary force, the hypothesis that segregation drives the evolution of sex has an important advantage over the hypothesis that recombination is the driving force. Namely, there is good evidence that deleterious mutations are typically partially recessive with weak to moderate selective effects (Simmons and Crow 1977; Deng and Lynch 1997; Charlesworth and Charlesworth 1999; Garcia-Dorado *et al.* 1999). In other words, data suggest that the form of one-locus fitness interactions is favorable to the evolution of sexual reproduction (see Figures 2–4). In contrast, there is little evidence that epistatic fitness interactions are weak and negative (Otto and Feldman 1997; Rice 2002), as required for genetic associations among loci to favor increased levels of recombination and sex (Barton 1995).

This article is predicated on the assumption that the organism in question is diploid. In haploid organisms, segregation within a locus is irrelevant, and there would be no indirect selection on a modifier of sex. The fact that sex is especially favorable with inbreeding begs the question of whether evolution would even maintain diploid life cycles. Models of life-cycle evolution indicate, however, that expansion of the diploid phase is favored when deleterious alleles are partially recessive and when beneficial alleles are partially dominant, even when inbreeding is present (Otto and Goldstein 1992; Orr and Otto 1994; Otto 1994; Jenkins and Kirkpatrick 1995; Otto and Marks 1996). Thus, the result of this article that sex with inbreeding is favored when selection is weak and $h < \frac{1}{2}$ is consistent with the assumption that the species remains diploid (see, especially, Otto and Marks 1996). Conversely, when $h > \frac{1}{2}$, life-cycle models predict that the predominant life-cycle phase should be haploid. Thus, although a second region was identified in which sex is favored (strong selection and $h > \frac{1}{2}$), the evolution of haploidy is favored in this second region, which would eliminate the advantages of segregation.

Turning this argument around, the fact that sex is favored by the advantages of segregation under realistic conditions (*i.e.*, when deleterious mutations are weakly selected and partially recessive and when inbreeding occurs) suggests that we should expect sex to evolve more frequently in organisms that primarily experience selection as diploids. At a broad taxonomic level, there is a correlation between the degree of diploidy and the relative level of sexuality (*i.e.*, the haploid phase is much reduced in vascular plants and animals, which have relatively low levels of asexual reproduction), but whether this correlation persists at a finer and more relevant taxonomic scale remains to be tested rigorously (see also Otto and Marks 1996).

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APPENDIX

Here I derive the expected persistence times of an association between a modifier allele and a viability allele. Let t_1 equal the expected number of generations (excluding the current generation) that a modifier allele remains associated with a viability allele currently on the same chromosome. Similarly, let t_2 equal the expected number of generations that a modifier allele remains associated with a viability allele currently on the homologous chromosome. t_1 and t_2 can be solved using branching processes to describe whether or not the associations persist from the current generation to the next. Observe that if, in the current generation, an organism does not have sex, then the association is expected to persist for a total of $t_1 + 1$ generations for alleles initially on the same chromosome and $t_2 + 1$ generations for alleles on homologous chromosomes, assuming that all else is equal in all generations. If the organism does have sex but recombination does not occur between the modifier and viability loci, then the association is expected to persist for a total of $t_1 + 1$ generations for alleles initially on the same chromosome and for 0 generations for alleles on homologous chromosomes, which segregate apart. If the organism does have sex and recombination does occur, then the association is expected to persist for a total of 0 generations for alleles initially on the same chromosome, which recombine and segregate away from each other, but for $t_1 + 1$ generations for alleles initially on homologous chromosomes, which have now recombined onto the same chromosome. Considering all of the above possibilities, we get two equations describing how the persistence times in the current generation are related to the persistence times in the next generation:

$$t_1 = (1 - \sigma_2)(t_1 + 1) + \sigma_2(1 - r)(t_1 + 1) + \sigma_2 r(0)$$
$$t_2 = (1 - \sigma_2)(t_2 + 1) + \sigma_2(1 - r)(0) + \sigma_2 r(t_1 + 1). \quad \text{(A1)}$$

These equations can be solved, yielding

$$t_1 = \frac{1 - \sigma_2 r_{MA}}{\sigma_2 r_{MA}}$$
$$t_2 = \frac{1 - \sigma_2/2}{\sigma_2/2}. \quad \text{(A2)}$$

Note that only the frequency of sex in *Mm* heterozygotes (σ_2) enters into the above equations because the modifier allele, *m*, is assumed to be rare and therefore always coupled to *M* in (31).